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The content of this letter has been agreed with the European Regulatory Authorities, including the Irish Medicines Board (IMB)

Dear Healthcare Professional,

IMPORTANT SAFETY INFORMATION CELANCE/Pergolide

Eli Lilly is writing to inform you of important safety information and changes to the prescribing information for CELANCE/pergolide prompted by reports of fibrotic reactions, including valvulopathy, in chronic users of ergot-derived dopamine receptor agonists. These changes have been agreed to by the Committee for Medicinal Products for Human Use (CHMP) during an EU referral procedure (EMEA/H/A-31/881) which reassessed the risk profile of ergot-derived dopamine receptor agonists.

Further information on the safety concern
Recent data from published literature suggest that higher doses and/or cumulative exposure of ergot-derived dopamine receptor agonists are risk factors for development of valvular pathology. Based on these findings, the Posology, Contra-indications, Warnings and Undesirable Effects sections of the Summary of Product Characteristics have been modified.

Changes to the Summary of Product Characteristics
The following points highlight the changes:

- The maximum dose of pergolide has been reduced from 5mg per day to 3mg per day.
- Before initiating treatment, all patients must undergo a cardiovascular evaluation, including echocardiogram.
- Evidence of cardiac valvulopathy, as determined by pre-treatment echocardiography, is a contra-indication.
- Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is now considered essential rather than recommended. Following treatment initiation, the first echocardiogram must occur within 3-6 months; thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment but must occur at least every 6 to 12 months.

- Cardiac valvulopathy (including regurgitation) and related cardiac disorders (pericarditis and pericardial effusion) are listed as very common undesirable effects.

Strict adherence to these requirements is important to protect patient safety.

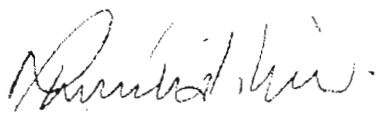
Healthcare Professionals are reminded that pergolide is indicated only as second line therapy in Parkinson's disease.

A copy of revised wording for sections of the Summary of Product Characteristics adopted by the CHMP is attached.

Call for reporting
Healthcare Professionals are reminded of the need to report suspected adverse reactions in accordance with the national spontaneous reporting system, to the IMB and/or the company in the usual way.

Communication information
Should you have any questions or concerns regarding this important safety information, please contact the Lilly Medical Information department on +44 (0) 1256 315 999.

Yours sincerely,



Dr Maurício Silva de Lima M.D., Ph.D.
UK & ROI Medical Director

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR PERGOLIDE CONTAINING MEDICINAL PRODUCTS

4.2 Posology and method of administration
The following should be reflected as appropriate:
Restriction of the maximum dose to 3 mg/day.

4.3 Contraindication:
...[ ]...
"Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography."

4.4 Special warnings and precautions for use:
...[ ]...
"Fibrosis and cardiac valvulopathy and possibly related clinical phenomena:
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin $5HT_{2B}$ receptor, such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.

There is evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology. However, valvulopathy and fibrotic reactions have been reported during treatment with pergolide at doses less than 0.5mg/day.

Before initiating treatment:
All patients must undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. In patients with valvular regurgitation, it is not known whether pergolide treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with pergolide (see section 4.3).

It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.

During treatment:
Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.

Therefore, during treatment, attention should be paid to the signs and symptoms of:

- *Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain.*
- *Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.*
- *Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.*

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Pergolide should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see Section 4.3).
The need for other clinical monitoring (e.g. physical examination including, cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder."

4.8 Undesirable effects:

The following should be included under Cardiac disorders:

"Very common: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)."